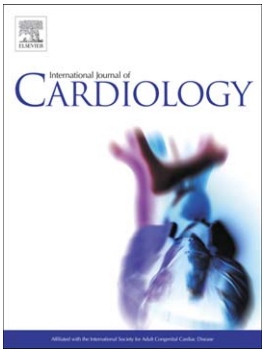

A comparison study of the echocardiographic changes in hypertensive patients treated with Telmisartan vs. Enalapril

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A comparison study of the echocardiographic changes in hypertensive patients treated with Telmisartan vs. Enalapril

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Abstract

Background: Hypertension-induced cardiac dysfunction is variable among the different anti-hypertensive medications. This study compares the effects of telmisartan and enalapril on the echocardiographic parameters in hypertensive patients.

Materials and methods: This was a randomised single blinded study. Eighty hypertensive patients were included in this study and they were randomly allocated into two study groups: Group 1 included 40 patients who were taken telmisartan 80mg once daily for six months. Group 2 included 40 patients who were taken enalapril, 20mg once daily for six months. An additional 40 healthy participants were enrolled in the study as controls (Group 3). Baseline echocardiographic scan was done at the start of the study and after 6 months of treatment including assessment of left ventricular systolic and diastolic function with assessment of left ventricular mass index, in addition to measurements of blood pressure, heart rate and double product.

Results: Both group 1 and group 2 (telmisartan and enalapril groups respectively) showed comparable statistically significant improvement in the diastolic functional parameters ($P<0.010$), while both medication didn't demonstrate changes in the systolic functional parameters. Furthermore, telmisartan was significantly effective in reducing the interventricular septal thickness and left ventricular mass index ($P<0.010$).

Conclusions: Both drugs interfere with renin-angiotensin aldosterone system, protecting the myocardium from high blood pressure. Findings from our study provide key results for physicians in deciding the appropriate antihypertensive drug for each patient depending based on the patient's intolerability for either medications.

Keywords: Hypertension; Left ventricular hypertrophy; Telmisartan; Enalapril; Echocardiography.

Introduction:

Hypertension can be defined as an elevated blood pressure of ≥140/90 mm Hg or reported current use of antihypertensive medications.[1]It is the most common comorbidity worldwide and a major public health problem for millions of people with more impact on the health welfare in many developing countries.[2] High blood pressure represents a major modifiable risk factor for cardiovascular diseases such as heart failure, heart attack, stroke, retinal haemorrhage, and an end-stage renal disease.[3]In most of these cases, there is no known underlying cause, however, pre-existing conditions (as endocrine or renal problems) can be attributed to its development and exacerbate its complications.[4]Long term hypertension results in thickening and loss of arterial wall elasticity leading to endothelial dysfunction with hypertrophy of the left heart ventricle due to an inevitable adaptation to increased hemodynamic load.[5,6]

Furthermore, endothelial dysfunction is considered to be a characteristic pathology of patients with essential hypertension and has been found to be associated with the development of coronary artery diseases and a risk factor for future cardiovascular events; however, the prognosis can be significantly improved by effective antihypertensive treatment.[7,8]Hypertensive patients with left ventricular hypertrophy (LVH) are at high risk of developing rhythmic, mechanical and ischemic cardiac complications, therefore antihypertensive drugs which reduce left ventricular hypertrophy are more effective in improving cardiovascular outcomes.[9,10]Principally, left ventricular hypertrophy is diagnosed by left ventricular mass (LVM) and left ventricular mass index (LVMI) in echocardiography.[11]Several antihypertensive treatments, especially angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, can reverse LVH and improve cardiovascular outcomes.[12,13]

Materials and Methods:

Patients recruitment: This study was approved by the Human Ethics Committee, College of Medicine, University of Kufa. Eighty hypertensive patients (average age 58±15 years) and forty normotensive controls (57±14 years) attending Al-Sadr Teaching Hospital in Al-Najaf, Iraq for the period between September 2013 and December 2015 were included in this study. Informed consent was obtained from all the participants before enrolling in this study.

Patients with essential hypertension were included when their diastolic blood pressure (DBP) was > 90 mmHg but less than 110 mmHg and systolic blood pressure (SBP) was > 140mm Hg but less than 180mm Hg. These patients were either previously untreated or they were off treatment. In all patients, supine BP was measured by a mercury sphygmomanometer using the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. The average of three measurements was used as the clinic blood pressure. These patients underwent full medical history evaluation and complete physical examination including measurement of body weight (in kg) and height (in cm) and body surface area (in m^2). The following categories of patients were excluded from the study: 1. Patients with diabetes mellitus. 2. Patients with history and/or signs of cardiovascular complications e.g. heart failure, myocardial infarction, angina pectoris and stroke. 3. Pregnancy or lactation. 4. Patients with major target organ damage e.g. serum creatinine > 1.5 mg/dL.5.Atrial fibrillation or other major arrhythmias. 6.Patients with secondary form of hypertension. 7. Patients with valvular heart disease. 8. Patients were also excluded if both echocardiographic apical and parasternal views were inadequate for obtaining measurements.

Participants patients included in the study were randomly allocated into two equal study groups (40 patients in each group). (Group 1) were given telmisartan 80mg tablet (Micardis® 80 mg, Boehringer Ingelheim, Germany), once daily, and group 2 received enalapril 20mg tablet (Renitec® 20mg, Merck Sharp & Dohme, Australia), once daily. The target is to keep blood pressure consistently below 140/90 mmHg. Forty normotensive controls received placebo. The patients together with the normotensive controls were studied and followed for 6 months. Hypertensive patients and the normotensive controls underwent full Echo-Doppler studies. Echocardiography was performed using diagnostic ultrasound system device (model Combison®/ 530 Voluson® 530D No: A 03790).

Measurement of blood pressure, heart rate and double product: At baseline blood pressure was measured using the standard cuff sphygmomanometer on two or three occasions before the study SBP, was read at the first Korotkoff sound and DBP at the disappearance of the Korotkoff sound (phase V). The means of all measurements were used for comparisons. At weekly follow up visits, blood pressure was measured with the same technique as at baseline and the goal was to keep the blood pressure consistently below 140/90 mm Hg. The heart rate was recorded before the treatment period and at each visit and the double product was calculated which is the product of SBP multiplied by the heart rate.

Assessment of left ventricular systolic function: To assess left ventricular systolic function, left ventricular ejection fraction and fractional shortening were measured. Fractional shortening (FS): This parameter reflects the relative change of left ventricular internal dimension throughout the cardiac cycle. It is measured as the ratio of the difference between end diastolic (EDd) and end systolic (ESd) internal diameters to the end diastolic internal diameter. This ratio is multiplied by 100 to obtain the percent fractional shortening % FS =

EDd–ESd/EDd x 100, it is the most commonly applied M-Mode derived measure of LV systolic function.[14] Ejection fraction (EF): It employs the percent change of LV volume instead of the percent change of LV internal dimension. It is calculated as the percent ratio of the difference between end diastolic volume (EDv) and end systolic volumes (ESv) to the end diastolic volume. % EF= EDv–ESv /EDv x 100.

Assessment of left ventricular diastolic function: To assess left ventricular diastolic function, a pulsed-wave Doppler transmitral flow velocity profile was obtained from the apical 4 chamber view, and the sample volume was positioned on the tips of mitral valve leaflets.[15] The following parameters were evaluated:

1. Peak E velocity (peak transmitral flow velocity in early diastole).
2. Peak A velocity (peak transmitral flow velocity in late diastole).
3. Mitral deceleration time (DT): The time from peak E wave to base line.
4. E/A ratio.
5. Isovolumic relaxation time (IVRT): The interval from aortic valve closure signal to mitral valve opening signal and was obtained by placing the sample volume at an intermediate point between the mitral and aortic valves.[15]All the measurements of diastolic function were derived from the average of 3 consecutive cardiac cycles.

Statistical analysis: Statistical analyses were performed by using SPSS (statistical package for social sciences) version 20 (IBM, USA). Data were expressed as mean ± SEM. Within-group changes from baseline to 6 months were analysed by the paired t–test and P-values equal or less than 0.05 were considered to be statistically significant. Comparisons among treatment groups of mean changes from baseline to 6 months were performed by Analysis of Variance (ANOVA). Pair wise comparisons of groups were made by using LSD statistic at a

significant P level of 0.01. Both patients and the radiologists were unable to identify the type of the current medication used.

Results

Out of the forty hypertensive patients initially enrolled in this study in each study group, thirty hypertensive patients continued in Group 1 to be treated with telmisartan (22 Male and 8 Female), and thirty hypertensive patients continued in Group 2 to be treated with enalapril (Group 2), (20 Male and 10 Female).

At baseline: The patient groups were comparable in age, degree of hypertension and base line Echo-Doppler findings, namely interventricular septal thickness (IVST), posterior wall thickness (PWT), LV internal diameter at systole (LVIDs), LV internal diameter at diastole (LVIDd), Left ventricular mass index (LVMI), ejection fraction (EF%), fractional shortening (FS%), maximum E wave velocity, maximum A wave velocity, E/A ratio, isovolumic relaxation time (IVRT) and deceleration time (Table 1).

Table (1A): Baseline echocardiographic parameters in hypertensive patients and normotensive control subjects. Data are expressed as mean ± SEM.

Echocardiographic parameter	Telmisartan (Group1)	Enalapril (Group 2)	Control (Group 3)	P value
Ventricular septal thickness (Mm)	16.47±0.66	16.60±0.52	10.09±0.18	<0.01
Posterior wall thickness (Mm)	13±0.53	13.20±0.55	9.48±0.23	<0.01
Left ventricular systolic diameter (Mm)	31.13±1.47	30.47±1.55	32.61±1.12	>0.05

Left ventricular diastolic diameter (Mm)	47.17±1.19	46.37±1.41	50.61±1.28	>0.05
LV mass index (g/m^2)	167.91±4.49	165.74±4.68	99.42±2.70	<0.01

By comparing the baseline values of hypertensive patients (Group 1 and Group 2) with the normotensive controls (Group 3), the following results were noticed:

1- A significantly higher IVST (16.47±0.66 Mm for telmisartan group and 16.60±0.52 Mm for enalapril group vs. 10.09±0.18 Mm in normotensive, P<0.01); PWT (13±0.53 Mm for telmisartan group and 13.20±0.55 Mm for enalapril group vs. 9.48±0.23 Mm in normotensive, P<0.01); And, LVMI (167.91±4.49 g/m^2 for telmisartan group and 165.74±4.68 g/m^2 for enalapril group vs. 99.42±2.70 g/m^2 in normotensive, P<0.01). Whereas LV systolic and diastolic end diameters were comparable between hypertensive and normotensive (Table 1).

2- A significantly less E wave velocity (74.65±3.15 cm/s for telmisartan group and 72.30±3.90 cm/s for enalapril group vs. 80.83±1.46 cm/s in normotensive, P<0.01); a significantly higher A wave velocity (80.97±2.40 cm/s for telmisartan group and 77.80±3.71 cm/s for enalapril group vs. 70.04±1.80 cm/s in normotensive, P<0.01); a significantly less E/A ratio (0.90±0.03 for telmisartan group and 0.94±0.05 for enalapril group vs. 1.15±0.03 in normotensive, P<0.01); a significantly higher IVRT (98.33±4.51 Ms for telmisartan group and 97.60±3.40 Ms for enalapril group vs. 74.17±1.47 Ms in normotensive, P<0.01); and, a significantly higher DT (220.16±4.95 Ms for telmisartan group and 223.67±8.88 Ms for enalapril group vs. 200.74±2.66 Ms in normotensive, P<0.01) in hypertensive patients (Table 2).

Diastolic functional parameter	Telmisartan (Group 1)	Enalapril group 2	Control (Group 3)	P value
E wave(cm/s)	74.65±3.15	72.30±3.90	80.83±1.46	<0.01
A wave(cm/s)	80.97±2.40	77.80±3.71	70.04±1.80	<0.01
E/A	0.90±0.03	0.94±0.05	1.15±0.03	<0.01
Isovolumic relaxation time (Ms)	98.33±4.51	97.60±3.40	74.17±1.47	<0.01
Deceleration time (Ms)	220.16±4.95	223.67±8.88	200.74±2.66	<0.01

Table (2): Baseline diastolic functional parameters in hypertensive patients and normotensive control subjects. Data are expressed as mean ± SEM.

3- There were no significant differences between the hypertensive groups (Group 1 and 2) and the normotensive controls (Group 3) in regards to the ejection fraction (EF%) and fractional shortening (FS %) values (Table 3).

Table (3): Baseline systolic functional parameters in hypertensive patients and normotensive control subjects. Data are expressed as mean ± SEM.

Systolic functional parameter	Telmisartan (Group 1)	Enalapril (Group 2)	Control (Group 3)	P value
Ejection fraction %	71.18±1.98	68.93±2.0	70.00±1.40	>0.05
Fractional shortening %	35.39±1.85	32.88±1.42	36.09±0.99	>0.05

The study also showed a significant reduction in the blood pressure and double product in both hypertensive study groups (Group 1 and Group 2). The telmisartan-treated group showed a significant reduction of SBP (156.5±2.09 mmHg vs. 135.33±1.07 mmHg, P<0.01), DBP (94.5±0.73 mmHg vs. 82.67±0.79 mmHg, P<0.01) and double product (11699.83±225.02 vs. 10391.17±130.90, P<0.01) whereas heart rate was not significantly changed (Table 4).

Table (4): Effects of telmisartan (80 mg daily) on blood pressure, heart rate and double product. Data are expressed as mean ± SEM.

	Before treatment	After treatment	P value
SBP, mm Hg	156.5±2.09	135.33±1.07	<0.01
DBP, mm Hg	94.5±0.73	82.67±0.79	< 0.01
Heart rate, beat/min	75.77±0.98	76.77±0.72	> 0.05
Double product	11699.83±225.02	10391.17±130.90	< 0.01

Group 2 also showed a significant reduction of the SBP (157.50±1.43 mmHg vs. 135.50±0.77 mmHg, p<0.01), DBP (97.17±0.57 mmHg vs. 80.50±0.65 mmHg, p<0.01) and the double product (12533±245.88 vs. 10764.83±140.73, P<0.01), while there were no significant changes in the heart rate (Table 5).

Table (5): Effects of enalapril (20 mg daily) on blood pressure, heart rate and double product. Data are expressed as mean ± SEM.

	Before treatment	After treatment	P value
SBP, mm Hg	157.50±1.43	135.50±0.77	<0.01
DBP, mm Hg	97.17±0.57	80.50±0.65	< 0.01

Heart rate, beat/min	78.47±0.96	78.90±0.79	> 0.05
Double product	12533±245.88	10764.83±140.73	< 0.01

Changes after 6 months of the antihypertensive (Telmisartan vs Enalapril) therapy: There were no significant differences between the effects of telmisartan and enalapril on SBP and heart rate. However, enalapril reduced DBP and double product slightly better than telmisartan (Figures 1 and 2).

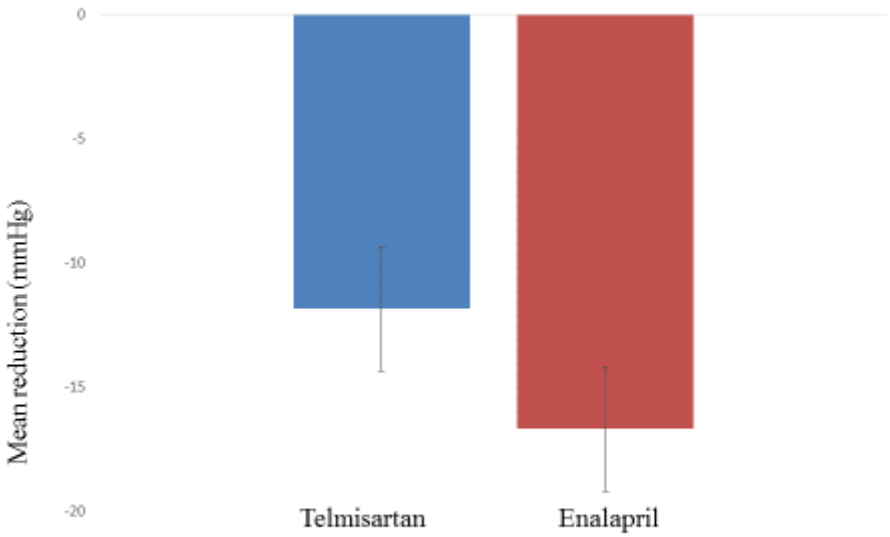

Figure (1): Mean change in diastolic blood pressure (mmHg) after six months treatment with daily telmisartan (80 mg) and enalapril (20 mg).

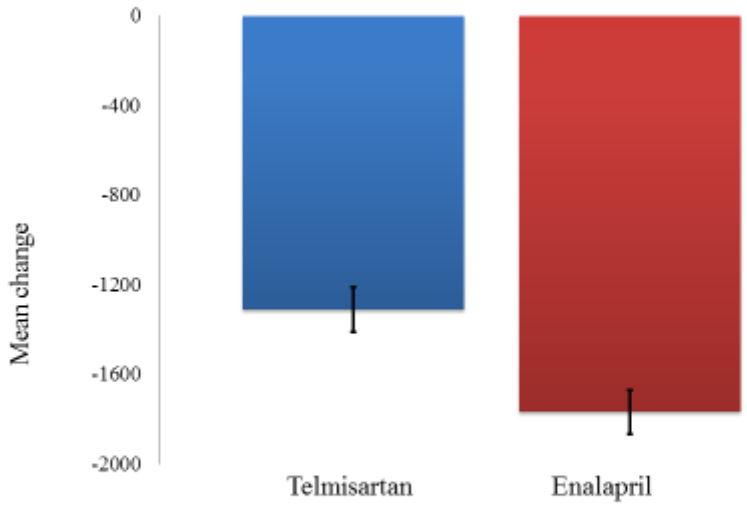

Figure (2): Mean change in double product after six months treatment with daily telmisartan(80 mg) and enalapril (20 mg).

In addition, there were no significant changes on left ventricular systolic functional parameters (ejection fraction and fractional shortening), after 6 months of the antihypertensive treatments.

Effects of treatment on LV diastolic function: In the telmisartan treated (Group 1), the maximum E wave velocity and the E/A ratio were significantly increased after 6 months of antihypertensive treatment (74.47±3.80 cm/s vs. 82.65±2.15 cm/s, P<0.01 for maximum E wave) and (0.90±0.03 vs. 1.15±0.05, P<0.01 for E/A ratio) respectively as shown in (table 6).

Table (6): Effects of telmisartan (80 mg daily) on left ventricular diastolic function. Data are expressed as mean ± SEM.

Diastolic functional parameter	Before treatment	After treatment	P value
E wave, cm/s	74.47±3.80	82.65±2.15	< 0.01
A wave, cm/s	80.97±2.40	71.23±2.69	< 0.01
E/A	0.90±0.03	1.15±0.05	< 0.01
Isovolumic relaxation time, Ms	98.33±4.50	84.00±3.69	< 0.01
Deceleration time, Ms	220.16±4.95	186.17±6.22	< 0.01

In addition, the maximum A wave velocity, deceleration time (DT) and the isovolumic relaxation time (IVRT) were significantly reduced by telmisartan after 6-months treatment (Table 6).

Table (7) presents the effects of enalapril on LV diastolic parameters and showing a significant increase in the maximum E wave velocity and E/A ratio after 6 months of the treatment. In addition, the maximum A wave velocity, DT and IVRT were also significantly reduced after 6 months of the treatment, table 7.

Table (7): Effects of enalapril (20 mg daily) on left ventricular diastolic function. Data are expressed as mean ± SEM.

Diastolic functional parameter	Before treatment	After treatment	P value
E wave, cm/s	75.73±2.40	82.30±2.90	< 0.01
A wave, cm/s	77.80±3.71	72.40±3.27	< 0.01
E/A	0.94±0.05	1.06±0.04	< 0.01

Isovolumic relaxation time, Ms	97.60±3.40	83.33±3.36	< 0.01
Deceleration time, Ms	223.67±8.88	191.33±5.97	< 0.01

Tolerability of the medication: Both of the medication used in this study were well tolerated with minimum or no side effects. Minor reported adverse events which were transient and disappeared with time and no patient had been withdrawn because of these side effects. List for the type and frequency of adverse events in each treated group are shown in Table 8.

Table (8): Adverse events reported during the study

Adverse event	Telmisartan group	Enalapril group
Dizziness	4 (13.3%)	2 (6.66%)
Headache	3 (10%)	2 (6.66%)
Fatigue	2 (6.66%)	3 (10%)
Impotence	1 (3.33%)	1 (3.33%)

Discussion:

Early recognition, prevention, and control of hypertensive diseases continue to be important goals for the national health policies and for the medical care decision makers. Moreover, there are disparities in the prevalence, treatment, and complications of hypertension among different countries all over the world.[16] To the best of our knowledge, this is the first study of its type to be done in the Middle East, which had clinically compared the effects of commonly used antihypertensive drugs (telmisartan vs. enalapril) in hypertensive patients on the heart structure and function.

It is worth to mention that all antihypertensive agents act by interfering with the normal mechanisms of blood pressure regulation. The renin-angiotensin aldosterone system (RAAS) is an important regulator of the blood pressure and the body fluid homeostasis in addition to the modulation of the vascular structure and function. Telmisartan and enalapril interfere with RAAS by different mechanisms and it's crucial to specify the effects of each drug on the cardiovascular system.

As a result of the long standing hypertension, an increase in the systemic vascular resistance and an increase in the vascular stiffness augment the load imposed on the left ventricle; this induces left ventricular hypertrophy and left ventricular diastolic dysfunction.[17] Normalisation of left ventricular mass emerged as a desirable goal of antihypertensive treatment.[18]In this study the Echo-Doppler studies revealed that the interventricular and the posterior wall thickness as well as the left ventricular mass index were statistically significantly greater in the hypertensive patients, while the end-diastolic diameters were comparable between the hypertensive participants and the normotensive controls. The systolic functional parameters namely the ejection fraction and the fractional shortening were comparable between the hypertensive participants and the controls. In addition, the diastolic functional parameters showed a statistically significantly higher A wave velocity, a significantly less E/A ratio, a significantly prolonged mitral deceleration time and isovolumic relaxation time among the hypertensive participants. These findings are related to the impaired relaxation of the left ventricle and it was in agreement with previous reports.[19,20]Both the systolic and diastolic BP values were significantly reduced after telmisartan and enalapril therapy. There were no significant changes in the heart rate in patients taking telmisartan and/or enalapril while the anti-hypertensive efficacy of both drugs

in patients with mild to moderate hypertension were comparable to what has been shown in the earlier studies.[21,22]

Double product is an indirect indicator of the myocardial oxygen demand and an index of the relative cardiac work. However, the double product is more strongly correlated with left ventricular mass than the mean daily blood pressure.[23] Echocardiographic LV hypertrophy is associated with a higher heart rate-systolic blood pressure double product.[24]Our study showed that both telmisartan and enalapril significantly decreased the double product in our patients. Similar findings were obtained by researchers in Lithuania and Japan.[25,26]

The hypertensive patients in this study had a good LV systolic function before treatment as evidenced by normal values of the ejection fraction and fractional shortening. After 6 months of treatment with telmisartan and/or enalapril therapy, the values of ejection and fractional shortening were not significantly changed and this was similar to that reported in other studies.[27,28]

Whether abnormalities of diastolic function are the earliest cardiac changes in hypertension is still a matter of dispute. In a previous study, they hypothesised that the earliest sign of cardiac involvement in hypertension is left ventricular structural abnormalities while left ventricular diastolic function is only marginally affected.[29] By contrast, Aeschbacher et al., 2001stated that diastolic dysfunction can be detected even before demonstrable left ventricular hypertrophy.[30] Diastolic dysfunction in patients with hypertension may present as a symptomatic findings on non-invasive testing, or as fulminant pulmonary oedema, despite normal left ventricular systolic function.[31] In hypertensive patients with non-coronary artery stenosis, the left ventricular myocardial diastolic dysfunction may be a determinant in the

impairment of the coronary microvascular vasodilatation capacity or a marker of silent ischaemia involving the microvascular circulation.[32]Improving the left ventricular diastolic dysfunction should therefore be one of the goals of the antihypertensive therapy.

In this study, treatment with telmisartan or enalapril resulted in an improvement of LV diastolic function, as evidenced by a significant rise of E/A ratio and a significant decrease of the deceleration time and isovolumic relaxation time (IVRT). Because a reduced E/A ratio predominantly revealed impaired relaxation,[33] it can be concluded that LV relaxation in particular could be improved by the drugs used in this study. This has been confirmed by measurements of IVRT, which revealed a prolonged relaxation at base line in all the groups that was decreased after antihypertensive drug treatment. The improvement in LV diastolic function is coincides with regression of LV hypertrophy. In patients with hypertension the beneficial effects of AT1 receptor antagonists losartan[34] and candesartan [35] on LV diastolic function has already been reported but not the effects of telmisartan. The finding of a significant increase of E/A ration in enalapril treated patients was similar to that previously reported.[36]

Similarity in such effects with both drugs could be attributed to their involvement in interfering activity with rennin-angiotensin system (RAS), although they are different in their mechanisms of action.

Conclusion, we have shown collections of echocardiographic parameters for hypertensive patients receiving either telmisartan or enalapril showing nearly similar pattern of effects possibly due to common pathway of action. Directions of future work could be towards comparison among different types of antihypertensive drugs that are working on other than RAS.

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Conflict of Interest

None declared.

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References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42(6):1206-52.

2. Colosia AD, Palencia R, and Khan S. Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. Diabetes Metab Syndr Obes. 2013;6:327-38.
3. CarreteroOA and Oparil S. Essential hypertension. Part I: definition and etiology. Circulation. 2000;101(3):329-35.
4. Sica DA. Endocrine causes of secondary hypertension. Journal of clinical hypertension (Greenwich, Conn) 2008;10:534-40.
5. Demede M, Pandey A, Innasimuthu L, Jean-Louis G, McFarlane SI, Ogedegbe G. Management of hypertension in high-risk ethnic minority with heart failure. Int J Hypertens. 2011;2011:417594.(doi): 10.4061/2011/417594. Epub 2011 May 25.
6. De Faire U and Prince J. Genes and environment behind ethnical differences in variations in left ventricular mass. J Hypertens. 2004;22(2):241-3.
7. DahlofB. Further evidence for low-dose combinations in patients with left ventricular hypertrophy. J Hum Hypertens. 2005;19(Suppl 1):S9-14.
8. Demede M, Pandey A, Innasimuthu L, Jean-Louis G, McFarlane SI, Ogedegbe G. A meta-analysis of the effects of treatment on left ventricular mass in essentialhypertension. Am J Med. 2003;115(1):41-6.
9. Cuspidi C, Lonati L, Macca G, Sampieri L, Fusi V, Michev I, Severgnini B, et al. Prevalence of left ventricular hypertrophy and carotid thickening in a large selected hypertensive population: impact of different echocardiographic and ultrasonographic diagnostic criteria. Blood Press. 2001;10(3):142-9.
10. Krauser DG, and Devereux RB. Ventricular hypertrophy and hypertension: prognostic elements and implications for management. Herz. 2006;31(4):305-16.

11. Faro GB, Menezes-Neto OA, Batista GS, Silva-Neto AP, Cipolotti R. Left ventricular hypertrophy in children, adolescents and young adults with sickle cell anemia. Revista brasileira de hematologia e hemoterapia 2015;37:324-8.

12. Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A, et al. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation. 2001;104(2):191-6.

13. Taddei S, Virdis A, Ghiadoni L, Sudano I, Salvetti A. Effects of antihypertensive drugs on endothelial dysfunction: clinical implications. Drugs. 2002;62(2):265-84.

14. Moon TJ, Miyamoto SD, Younoszai AK, Landeck BF. Left ventricular strain and strain rates are decreased in children with normal fractional shortening after exposure to anthracycline chemotherapy. Cardiology in the young 2014;24:854-65.

15. Prinz C, Lehmann R, Brandao da Silva D, et al. Echocardiographic particle image velocimetry for the evaluation of diastolic function in hypertrophic nonobstructive cardiomyopathy. Echocardiography (Mount Kisco, NY) 2014;31:886-94.

16. ErdineS, and Aran SN. Current status of hypertension control around the world. Clin Exp Hypertens. 2004;26(7-8):731-8.

17. Howell SJ, Sear JW, and Foex P. Hypertension, hypertensive heart disease and perioperative cardiac risk. Br J Anaesth. 2004;92(4):570-83.

18. SchmiederRE, and Messerli FH. Hypertension and the heart. J Hum Hypertens., 2000;14(10-11):597-604.

19. Mansencal N, Bordachar P, Chatellier G, Redheuil A, Diebold B, Abergel E.Comparison of accuracy of left ventricular echocardiographic measurements by fundamental imaging versus second harmonic imaging. Am J Cardiol, 2003;91(8):1037-9.

20. Hildick-Smith DJ, and Shapiro LM. Echocardiographic differentiation of pathological and physiological left ventricular hypertrophy. Heart. 2001;85(6):615-9.

21. Nedogoda SV, Ledyaeva AA, Chumachok EV, et al. Randomized trial of perindopril, enalapril, losartan and telmisartan in overweight or obese patients with hypertension. Clin Drug Investig 2013;33:553-61.

22. Yokota T, Osanai T, Hanada K, et al. Effects of telmisartan on markers of ventricular remodeling in patients with acute myocardial infarction: comparison with enalapril. Heart and vessels 2010;25:460-8.

23. Neto GR, Sousa MS, Costa ESGV, Gil AL, Salles BF, Novaes JS. Acute resistance exercise with blood flow restriction effects on heart rate, double product, oxygen saturation and perceived exertion. Clinical physiology and functional imaging 2016;36:53-9.

24. Mehta SK. Left ventricular mass by echocardiographic measures in children and adolescents. Cardiology in the young 2013;23:727-37.

25. Sakalyte G, Kavoliūniene A, Vainoras A, Jurkevicius R. Hypotensive effects of telmisartan on blood pressure during rest and exercise in patients with mild and moderate arterial hypertension. Medicina (Kaunas). 2002;38(9):901-9.

26. Mohri M, Tagawa H, Egashira K, Takeshita A. Intracoronary enalaprilat improves metabolic coronary vasodilation in patients with idiopathic dilated cardiomyopathy. J Cardiovasc Pharmacol. 2000;35(2):249-55.

27. Fountoulaki K, Dimopoulos V, Giannakoulis J, Zintzaras E, Triposkiadis F. Left ventricular mass and mechanics in mild-to-moderate hypertension: effect of nebivolol versus telmisartan. Am J Hypertens. 2005;18(2 Pt 1):171-7.

28. Fujii M, Wada A, Tsutamoto T, Ohnishi M, Isono T, Kinoshita M. Bradykinin improves left ventricular diastolic function under long-term angiotensin-converting enzyme inhibition in heart failure. Hypertension. 2002;39(5):952-7.

29. Palatini P, Frigo G, Vriz O, Bertolo O, Dal Follo M, Daniele L,et al. Early signs of cardiac involvement in hypertension. Am Heart J. 2001;142(6):1016-23.

30. Aeschbacher BC, Hutter D, Fuhrer J, Weidmann P, Delacrétaz E, Allemann Y. Diastolic dysfunction precedes myocardial hypertrophy in the development of hypertension. Am J Hypertens. 2001;14(2):106-13.

31. PhillipsRA, and Diamond JA. Diastolic function in hypertension. Curr Cardiol Rep. 2001;3(6):485-97.

32. Galderisi M, Cicala S, De Simone L, Caso P, Petrocelli A, Pietropaolo L, et al. Impact of myocardial diastolic dysfunction on coronary flow reserve in hypertensive patients with left ventricular hypertrophy. Ital Heart J. 2001;2(9):677-84.

33. Lavine SJ, Al Balbissi K. Adverse Cardiac Events and the Impaired Relaxation Left Ventricular Filling Pattern. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2016. (doi: 10.1016/j.echo.2016.02.008).

34. Fogari R, Mugellini A, Destro M, et al. Losartan and amlodipine on myocardial structure and function: a prospective, randomized, clinical trial. Diabet Med 2012;29:24-31.

35. Isobe N, Taniguchi K, Oshima S, Ono Z, Adachi H, Toyama T, et al. Candesartan cilexetil improves left ventricular function, left ventricular hypertrophy, and endothelial function in patients with hypertensive heart disease. Circ J. 2002;66(11):993-9.

36. Gonzalez GE, Wilensky L, Cassaglia P, Morales C, Gelpi RJ. Early administration of Enalapril prevents diastolic dysfunction and ventricular remodeling in rabbits with

myocardial infarction. Cardiovascular pathology: the official journal of the Society for Cardiovascular Pathology 2016;25:208-13.